

WHAT IS CLAIMED IS:

1. A method of increasing muscle function in a subject, said method comprising administering to said subject an agent selected from the group consisting of:

5 (a) a growth hormone (GH) secretagogue; and
(b) a composition comprising a GH secretagogue and a pharmaceutically acceptable carrier.

10 2. The method of claim 1, wherein said GH secretagogue is selected from the group consisting of a GH-releasing factor (GRF) and a GRF analog.

15 3. The method of claim 2 wherein said GRF analog is a GRF analog of formula A:

X-GRF Peptide (A)

wherein;

20 the GRF peptide is a peptide of formula B;

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-
A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-
Arg-A30-R0 (B)

25

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

30 A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

49

A25 is Asp or Glu;

A27 is Met, Ile or Nle

A28 is Ser or Asn;

A30 is a bond or amino acid sequence of 1 up to 15 residues; and

5

R0 is NH₂ or NH-(CH₂)_n-CONH₂, with n=1 to 12; and

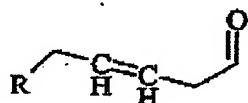
X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and the hydrophobic tail defining a backbone of 5 to 7 atoms;

10 wherein the backbone can be substituted by C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₆₋₁₂ aryl and the backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

15 said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C₃₋₉ cycloalkyl, and C₆₋₁₂ aryl.

20 4. The method of claim 3, wherein X is selected from the group consisting of:

25



1 (R=H or CH₃ or CH₂CH₃)
cis or *trans*



2 (R=H or CH₃ or CH₂CH₃)



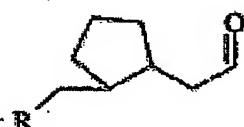
3 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures



4 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



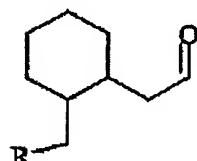
5 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)



6 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

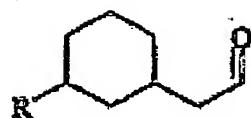
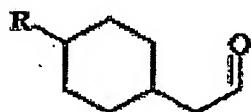
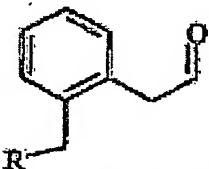
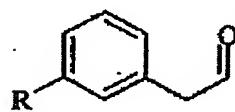
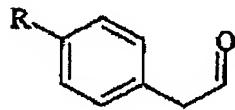
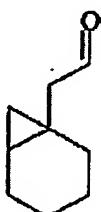


7 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)
 both as racemic mixtures
 or pure enantiomeric pairs



8 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

51

9 (R=H or CH₃ or CH₂CH₃)*cis* or *trans*, (when R ≠ H)both as racemic mixtures
or pure enantiomeric pairs10 (R=H or CH₃ or CH₂CH₃)*cis* or *trans*, (when R ≠ H)11 (R=H or CH₃ or CH₂CH₃)12 (R=H or CH₃ or CH₂CH₃)13 (R=H or CH₃ or CH₂CH₃) and

14

5. The method of claim 3, wherein A30 is selected from the group consisting of:

- (a) a bond;
- 5 (b) an amino acid sequence corresponding to positions 30-44 of a natural GRF peptide, and
- (c) said amino acid sequence of (b) having a 1-14 amino acid deletion from its C-terminus.

10 6. The method of claim 3, wherein said GRF peptide is selected from the group consisting of:

- (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 3;
- (b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 5; and
- 15 (c) said polypeptide of (a) having a 1 to 14 amino acid deletion from its C-terminus.

7. The method of claim 2, wherein said GRF analog is
20 (hexenoyl trans-3)hGRF(1-44)NH₂ (SEQ ID NO: 7).

8. The method of claim 1, wherein said muscle function is selected from the group consisting of:

- (a) muscle strength;
- 25 (b) muscle endurance; and
- (c) both (a) and (b).

9. The method of claim 8, wherein said muscle function is muscle strength.

30

10. The method of claim 9, wherein said muscle strength is peripheral muscle strength.

11. The method of claim 8, wherein said muscle function is muscle endurance.

12. The method of claim 1, wherein said increase results in
5 a reduction of a parameter selected from the group consisting of:

- (a) breathing discomfort;
- (b) leg discomfort; and
- (c) both (a) and (b).

10

13. The method of claim 1, wherein said increase results in an increase in lean body mass in said subject.

14. The method of claim 1, wherein said increase results in
15 a decrease in fat mass in said subject.

15. The method of claim 1, wherein the subject suffers from wasting.

20 16. The method of claim 15, wherein said wasting is associated with a condition selected from the group consisting of chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, human immunodeficiency virus infection, acquired immunodeficiency syndrome, cancer, malnutrition, 25 frailty, immobilization paraplegia and spinal disorder.

17. The method of claim 1, wherein said subject suffers from severe wasting.

30

18. The method of claim 17, wherein said subject has a body mass index less than or equal to 20.

19. The method of claim 17, wherein said subject has a weight less than 90% of ideal body weight.
20. The method of claim 17, wherein said subject is a male and said subject has a fat free mass index less than or equal to 16.
21. The method of claim 17, wherein said subject is a female and said subject has a fat free mass index less than or equal to 15.
22. The method of claim 1, wherein said agent is administered through a route selected from the group consisting of intravenous, oral, transdermal, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical.
23. The method of claim 1, wherein said GH secretagogue is administered in a dose from about 0.0001 mg to about 4 mg.
24. The method of claim 1, wherein said GH secretagogue is administered in a dose selected from the group consisting of about 1 mg and about 2 mg.
25. Use of an agent selected from the group consisting of:
 - (a) a growth hormone (GH) secretagogue; and
 - (b) a composition comprising a GH secretagogue and a pharmaceutically acceptable carrier;for increasing muscle function in a subject.

55

26. The use of claim 25, wherein said GH secretagogue is selected from the group consisting of a GH-releasing factor (GRF) and a GRF analog.

5 27. The use of claim 26, wherein said GRF analog is a GRF analog of formula A:

X-GRF Peptide (A)

10 wherein;

the GRF peptide is a peptide of formula B;

15 A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-
A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-
Arg-A30-R0 (B)

wherein,

20 A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

25 A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle

A28 is Ser or Asn;

30 A30 is a bond or amino acid sequence of 1 up to 15 residues; and

R0 is NH₂ or NH-(CH₂)_n-CONH₂, with n=1 to 12; and

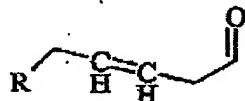
56

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and the hydrophobic tail defining a backbone of 5 to 7 atoms;

5 wherein the backbone can be substituted by C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₆₋₁₂ aryl and the backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

10 said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C₃₋₉ cycloalkyl, and C₆₋₁₂ aryl.

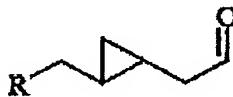
28. The use of claim 27, wherein X is selected from the
15 group consisting of:



1 (R=H or CH₃ or CH₂CH₃)
cis or *trans*



2 (R=H or CH₃ or CH₂CH₃)



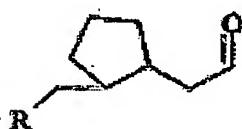
3 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



4 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



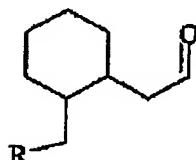
5 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)



6 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

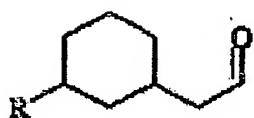


7 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)
 both as racemic mixtures
 or pure enantiomeric pairs

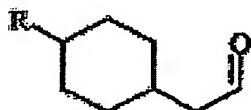


8 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

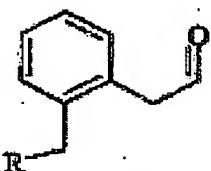
58



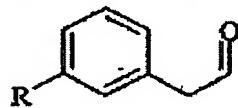
9 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)
 both as racemic mixtures
 or pure enantiomeric pairs



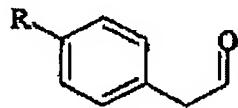
10 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)



11 (R=H or CH₃ or CH₂CH₃)



12 (R=H or CH₃ or CH₂CH₃)



13 (R=H or CH₃ or CH₂CH₃) and



14

29. The use of claim 27, wherein A30 is selected from the group consisting of:

- (a) a bond;
- 5 (b) an amino acid sequence corresponding to positions 30-44 of a natural GRF peptide, and
- (c) said amino acid sequence of (b) having a 1-14 amino acid deletion from its C-terminus.

10 30. The use of claim 27, wherein said GRF peptide is selected from the group consisting of:

- (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 3;
- (b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 5; and
- 15 (c) said polypeptide of (a) having a 1 to 14 amino acid deletion from its C-terminus.

31. The use of claim 26, wherein said GRF analog is
20 (hexenoyl trans-3)hGRF(1-44)NH₂ (SEQ ID NO: 7).

32. The use of claim 25, wherein said muscle function is selected from the group consisting of:

- (a) muscle strength;
- 25 (b) muscle endurance; and
- (c) both (a) and (b).

33. The use of claim 32, wherein said muscle function is muscle strength.

30

34. The use of claim 33, wherein said muscle strength is peripheral muscle strength.

60

35. The use of claim 32, wherein said muscle function is muscle endurance.

36. The use of claim 25, wherein said increase results in a
5 reduction of a parameter selected from the group consisting of:

- (a) breathing discomfort;
- (b) leg discomfort; and
- (c) both (a) and (b).

10

37. The use of claim 25, wherein said increase results in an increase in lean body mass in said subject.

38. The use of claim 25, wherein said increase results in a
15 decrease in fat mass in said subject.

39. The use of claim 25, wherein said subject suffers from wasting.

20 40. The use of claim 39, wherein said wasting is associated with a condition selected from the group consisting of chronic obstructive pulmonary disease, chronic renal failure, congestive heart failure, human immunodeficiency virus infection, acquired immunodeficiency syndrome, 25 cancer, malnutrition, frailty, immobilization paraplegia and spinal disorder.

41. The use of claim 25, wherein said subject suffers from severe wasting.

30

42. The use of claim 41, wherein said subject has a body mass index less than or equal to 20.

43. The use of claim 41, wherein said subject has a weight less than 90% of ideal body weight.

44. The use of claim 41, wherein said subject is a male and 5 said subject has a fat free mass index less than or equal to 16.

45. The use of claim 41, wherein said subject is a female and said subject has a fat free mass index less than or 10 equal to 15.

46. The use of claim 25, wherein said agent is adapted for an administration route selected from the group consisting of intravenous, oral, transdermal, 15 subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical.

47. The use of claim 25, wherein said GH secretagogue is adapted for administration in a dose from about 0.0001 20 mg to about 4 mg.

48. The use of claim 25, wherein said GH secretagogue is adapted for administration in a dose selected from the group consisting of about 1 mg and about 2 mg.

25 49. Use of an agent selected from the group consisting of:
(a) a growth hormone (GH) secretagogue; and
(b) a composition comprising a GH secretagogue and a pharmaceutically acceptable carrier;
30 for the manufacture of a medicament for increasing muscle function in a subject.

50. A package comprising:
(i) an agent selected from the group consisting of:

62

(a) a growth hormone (GH) secretagogue; and
(b) a composition comprising a GH secretagogue and a pharmaceutically acceptable carrier; and

5 (ii) instructions for increasing muscle function in a subject.

51. The package of claim 50, wherein said GH secretagogue is selected from the group consisting of a GH-releasing factor (GRF) and a GRF analog.

10

52. The package of claim 51, wherein said GRF analog is a GRF analog of formula A:

15 X-GRF Peptide (A)

wherein;

20 the GRF peptide is a peptide of formula B;

25 A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-
A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-
Arg-A30-R0 (B)

30 wherein,

35 A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

A27 is Met, Ile or Nle

A28 is Ser or Asn;

63

A30 is a bond or amino acid sequence of 1 up to 15 residues; and

R0 is NH₂ or NH-(CH₂)_n-CONH₂, with n=1 to 12; and

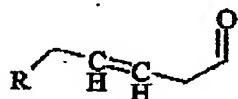
5

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and the hydrophobic tail defining a backbone of 5 to 7 atoms;

10 wherein the backbone can be substituted by C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₆₋₁₂ aryl and the backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

15 said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C₃₋₉ cycloalkyl, and C₆₋₁₂ aryl.

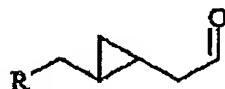
53. The package of claim 52, wherein X is selected from the
20 group consisting of:



1 (R=H or CH₃ or CH₂CH₃)
cis or *trans*



2 (R=H or CH₃ or CH₂CH₃)



3 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



4 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



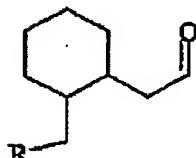
5 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R \neq H)



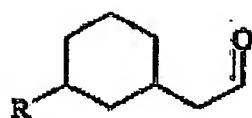
6 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



7 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R \neq H)
 both as racemic mixtures
 or pure enantiomeric pairs



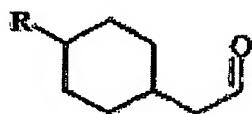
8 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



9 (R=H or CH₃ or CH₂CH₃)

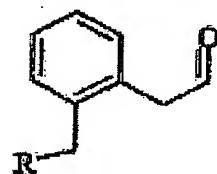
cis or *trans*, (when R ≠ H)

both as racemic mixtures
or pure enantiomeric pairs



10 (R=H or CH₃ or CH₂CH₃)

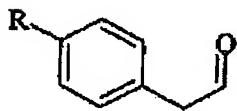
cis or *trans*, (when R ≠ H)



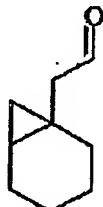
11 (R=H or CH₃ or CH₂CH₃)



12 (R=H or CH₃ or CH₂CH₃)



13 (R=H or CH₃ or CH₂CH₃) and



54. The package of claim 52, wherein A30 is selected from the group consisting of:

- (a) a bond;
- 5 (b) an amino acid sequence corresponding to positions 30-44 of a natural GRF peptide, and
- (c) said amino acid sequence of (b) having a 1-14 amino acid deletion from its C-terminus.

10 55. The package of claim 52, wherein said GRF peptide is selected from the group consisting of:

- (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 3;
- (b) a polypeptide comprising the amino acid sequence of SEQ ID NO: 5; and
- 15 (c) said polypeptide of (a) having a 1 to 14 amino acid deletion from its C-terminus.

20 56. The package of claim 51, wherein said GRF analog is (hexenoyl trans-3)hGRF(1-44)NH₂ (SEQ ID NO: 7).

57. The package of claim 50, wherein said muscle function is selected from the group consisting of:

- (a) muscle strength;
- 25 (b) muscle endurance; and
- (c) both (a) and (b).

30 58. The package of claim 57, wherein said muscle function is muscle strength.

59. The package of claim 58, wherein said muscle strength is peripheral muscle strength.

67

60. The package of claim 57, wherein said muscle function is muscle endurance.

5 61. The package of claim 50, where said increase results in a reduction of a parameter selected from the group consisting of:

- (a) breathing discomfort;
- (b) leg discomfort; and
- (c) both (a) and (b).

10

62. The package of claim 50, wherein said increase results in an increase in lean body mass in said subject.

15 63. The package of claim 50, wherein said increase results in a decrease in fat mass in said subject.

64. The package of claim 50, wherein said subject suffers from wasting.

20 65. The package of claim 64, wherein said wasting is associated with a condition selected from the group consisting of chronic obstructive pulmonary disease (COPD), chronic renal failure, congestive heart failure, human immunodeficiency virus infection, acquired 25 immunodeficiency syndrome, cancer, malnutrition, frailty, immobilization paraplegia and spinal disorder.

66. The package of claim 50, wherein said subject suffers from severe wasting.

30

67. The package of claim 66, wherein said subject has a body mass index less than or equal to 20.

68. The package of claim 66, wherein said subject has a weight less than 90% of ideal body weight.

5 69. The package of claim 66, wherein said subject is a male and said subject has a fat free mass index less than or equal to 16.

10 70. The package of claim 66, wherein said subject is a female and said subject has a fat free mass index less than or equal to 15.

15 71. The package of claim 50, wherein said agent is adapted for an administration route selected from the group consisting of intravenous, oral, transdermal, subcutaneous, mucosal, intramuscular, intranasal, intrapulmonary, parenteral, intrarectal and topical.

20 72. The package of claim 50, wherein said GH secretagogue is adapted for administration in a dose between about 0.0001 mg to about 4 mg.

25 73. The package of claim 50, wherein said GH secretagogue is adapted for administration in a dose selected from the group consisting of about 1 mg and about 2 mg.

74. A composition for increasing muscle function in a subject, said composition comprising:

- (a) a growth hormone (GH) secretagogue; and
- (b) a pharmaceutically acceptable carrier.

30 75. The composition of claim 74, wherein said GH secretagogue is selected from the group consisting of a GH-releasing factor (GRF) and a GRF analog.

76. The composition of claim 75, wherein said GRF analog is a GRF analog of formula A:

5

X-GRF Peptide (A)

wherein;

the GRF peptide is a peptide of formula B;

10

A1-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-Tyr-Arg-Lys-A13-Leu-A15-Gln-Leu-A18-Ala-Arg-Lys-Leu-Leu-A24-A25-Ile-A27-A28-Arg-A30-R0 (B)

15

wherein,

A1 is Tyr or His;

A2 is Val or Ala;

A8 is Asn or Ser;

20

A13 is Val or Ile;

A15 is Ala or Gly;

A18 is Ser or Tyr;

A24 is Gln or His;

A25 is Asp or Glu;

25

A27 is Met, Ile or Nle

A28 is Ser or Asn;

A30 is a bond or amino acid sequence of 1 up to 15 residues; and

30

R0 is NH₂ or NH-(CH₂)_n-CONH₂, with n=1 to 12; and

X is a hydrophobic tail anchored via an amide bond to the N-terminus of the peptide and the hydrophobic tail defining a backbone of 5 to 7 atoms;

35

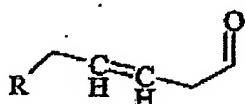
70

wherein the backbone can be substituted by C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₆₋₁₂ aryl and the backbone comprises at least one rigidifying moiety connected to at least two atoms of the backbone;

5

said moiety selected from the group consisting of double bond, triple bond, saturated or unsaturated C₃₋₉ cycloalkyl, and C₆₋₁₂ aryl.

10 77. The composition of claim 76, wherein X is selected from the group consisting of:



1 (R=H or CH₃ or CH₂CH₃)
cis or *trans*



2 (R=H or CH₃ or CH₂CH₃)



3 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
or pure enantiomeric pairs



4 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs



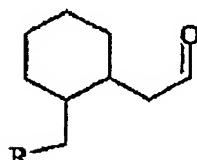
5 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)



6 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

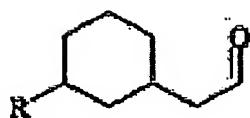
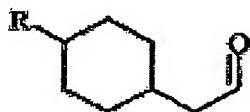
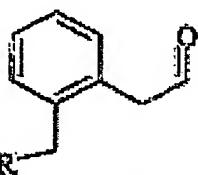
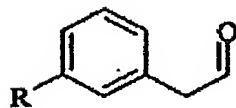
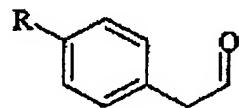


7 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, (when R ≠ H)
 both as racemic mixtures
 or pure enantiomeric pairs



8 (R=H or CH₃ or CH₂CH₃)
cis or *trans*, both as racemic mixtures
 or pure enantiomeric pairs

72

9 (R=H or CH₃ or CH₂CH₃)cis or trans, (when R \neq H)both as racemic mixtures
or pure enantiomeric pairs10 (R=H or CH₃ or CH₂CH₃)cis or trans, (when R \neq H)11 (R=H or CH₃ or CH₂CH₃)12 (R=H or CH₃ or CH₂CH₃)13 (R=H or CH₃ or CH₂CH₃) and

14

78. The composition of claim 76, wherein A30 is selected from the group consisting of:

- (a) a bond;
- 5 (b) an amino acid sequence corresponding to positions 30-44 of a natural GRF peptide, and
- (c) said amino acid sequence of (b) having a 1-14 amino acid deletion from its C-terminus.

10 79. The composition of claim 76, wherein said GRF peptide is selected from the group consisting of:

- (a) a polypeptide comprising the amino acid sequence of SEQ ID NO: 3;
- (b) a polypeptide comprising the amino acid sequence of 15 SEQ ID NO: 5; and
- (c) the polypeptide of (a) having a 1 to 14 amino acid deletion from its C-terminus.

20 80. The composition of claim 75, wherein said GRF analog is (hexenoyl trans-3)hGRF(1-44)NH₂ (SEQ ID NO: 7).